

# **EXHIBIT 39**



# Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk

*Part 2: Initiating a Trial  
of Opioid Therapy*



## Advances in Opioid Analgesia: Maximizing Benefit While Minimizing Risk

### OVERVIEW

The National Initiative on Pain Control® (NIPC®) is dedicated to helping physicians and other healthcare professionals maximize pain management strategies for their patients.

### SPONSOR

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Thomson Professional Postgraduate Services® is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

### GRANTOR

The NIPC® and this activity are supported by an unrestricted educational grant from Endo Pharmaceuticals Inc.

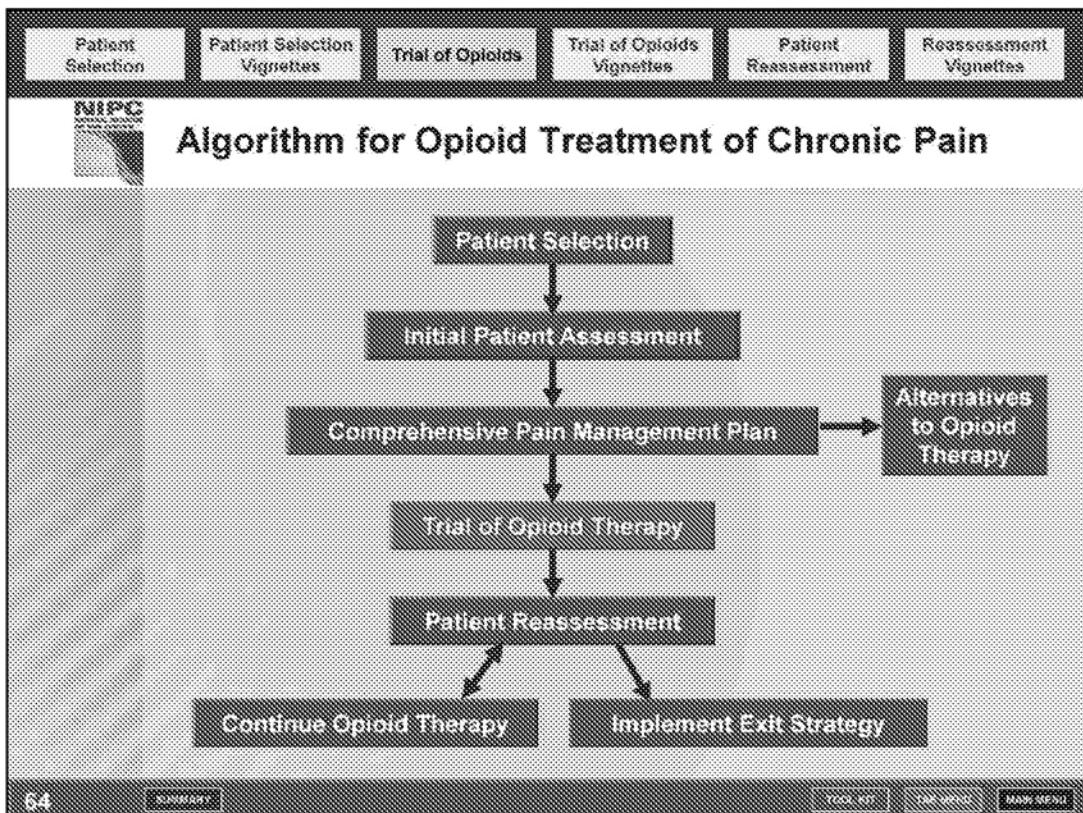
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## Educational Objective

Part 2: Initiating a Trial of Opioid Therapy

- » **Initiate a trial of opioid therapy and assess ongoing risks and benefits in treatment of the chronic pain patient**



This algorithm has been created to assist in decision making about opioid therapy for chronic pain. This algorithm will be repeated throughout this module at each point at which a decision is to be made. Not only is the participant guided through patient selection and assessment, but also is shown what to consider in starting a trial of opioids, alternatives to opioid therapy, ongoing reassessment, developing an exit strategy, as well as conversion and rotation as part of the treatment strategy.

The participant will be guided through the algorithm using highlighted text and arrows to identify decision points; then each part of the algorithm will be expanded upon in each section that follows.

The first section to be discussed is Patient Selection.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**Ground Rules for Prescribing Opioid Analgesics**

- » Proper patient selection is *THE* key
- » Proper patient assessment is mandatory
- » Opioid analgesics are but one component of a comprehensive treatment plan
- » Prescribing opioids on a trial basis *MUST* be monitored
- » Patient reassessment is *KEY* to ongoing monitoring of opioid therapy
- » Any medical treatment can be continued, discontinued, or modified

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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## Questions to Consider Before Initiating a Trial of Opioid Therapy

- What pain syndromes are appropriate for opioid analgesia?
- What patients are appropriate candidates for opioid analgesia?
- Should opioids be the first analgesic class prescribed?
- What patients are at high risk for abuse and diversion of opioids?

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## Set Realistic Goals

- » Reach agreement with patient on shared goals of treatment
- » Complete pain relief rarely achieved
- » Common goals include
  - pain reduction
  - improvement in selected areas of function
  - improved mind-set
  - improved work

66      **SUMMARY**      **GOALS**      **TOPIC INDEX**      **HOME MENU**

Clearly define Scope of Treatment.

While total analgesia may be the ideal, more realistic goals would be pain amelioration and improved function.

Partner with the patient.

Both doctor and patient have unique responsibilities.

Agreement is consensual, not obligatory.

Both doctor and patient must be open to negotiation.

Patient needs to understand the pros and cons of the therapy.

Patient agrees to follow the treatment plan.

Both physician and patient must gain something in the encounters.

Quill TE. Partnerships in patient care: a contractual approach. *Ann Intern Med.* 1983;98:228-234.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NIPC**  **SOAPP® Tool Predicts Patient Responsiveness to Opioid Medication**

**The Screener and Opioid Assessment for Patients with Pain® (SOAPP®)**

- » Evaluates patient's relative risk for developing problems on long-term opioid therapy
- » Brief 5-item questionnaire
- » More specific 24-item questionnaire available
- » Quick to complete in <5 minutes
- » Easy to score on a 5-point scale
- » Documents level of patient monitoring required
- » Developed based on expert consensus
- » Longer version available in the *Opioid Analgesia Tool Kit*

SOAPP®

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Many clinicians remain reluctant to prescribe opioid medications due to concerns about addiction, misuse, and other aberrant medication-related behaviors, as well as concerns about liability and censure.

**The Screener and Opioid Assessment for Patients with Pain<sup>SM</sup> (SOAPP<sup>SM</sup>) Version 1.0** will help determine which patients are likely to be manageable in a primary care setting, versus those who would likely do best in a specialty setting with more intensive patient monitoring and management capabilities. For additional information, a link to the Web site PainEDU.org is provided on the CD-ROM.

The slide is titled "Patient Education Helps Compliance". It features a bulleted list of three items on the left:

- » Provide written materials about opioid therapy to patient and family
- » Debunk myths about tolerance, dependence, and addiction
- » Patient education brochures available in Opioid Analgesia Tool Kit

To the right of the list is a graphic of the "Opioid Analgesia Tool Kit". The kit includes several brochures:

- Understanding Your Pain
- Taking Oral Opioid Analgesics
- Using a Pain Rating Scale

At the bottom of the slide are navigation buttons: "68", "SUMMARY", "CONTINUE", "HOME", and "PRINT".

One study of patient-control analgesia (PCA) with morphine found that patients wanted to know that the drug used in PCA was morphine. They wanted more information about side effects, needed to be reassured that it was safe, and that they could not overdose or become addicted. They wanted detailed instructions and diagrams about the technique.

Some of the misconceptions concerning long-term use of opioids in nonmalignant pain relate to the inappropriate use of the terms “tolerance” and “addiction.” Analgesic tolerance, which is very uncommon in the clinical setting, is a phenomenon in which exposure to the opioid itself causes the patient who has achieved analgesia to require a higher dosage to maintain the same level of effect. A need for dose escalation results from factors other than tolerance, including disease progression. Addiction is an association of psychological dependence and aberrant drug-related behaviors. Addiction to opioids in the context of acute pain treatment is rare in those with no history of addictive disorder. Clinicians need to become aware of the new findings regarding the low risk of addiction and tolerance in this setting. However, more studies need to be made to determine the risk of addiction for chronic pain treatment. Drug dependence is a separate phenomenon that is avoidable by not suddenly discontinuing opioid therapy and should not be confused with addiction.

Anderson KO, Richman SP, Hurley J et al. Cancer pain management among underserved minority outpatients: perceived needs and barriers to optimal control. *Cancer*. 2002;94:2295-2304.

Berry PE, Ward SE. Barriers to pain management in hospice: a study of family caregivers. *Hosp J*. 1995;10:19-33.

Chumbley GM, Hall GM, Salmon P. Patient-controlled analgesia: what information does the patient want? *J Adv Nurs*. 2002;39:459-471.

Paice JA, Toy C, Shott S. Barriers to cancer pain relief: fear of tolerance and addiction. *J Pain Symptom Manage*. 1998;16:1-9.

Portenoy RK, Savage SR. Clinical realities and economic considerations: special therapeutic issues in intrathecal therapy--tolerance and addiction. *J Pain Symptom Manage*. 1997;14(suppl 3):S27-S35.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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## Patient Care Agreement/Informed Consent Components

- » **Reminder: opioids are one modality in multifaceted approach to achieving goals of therapy**
- » **Detailed outline of procedures and expectations between patient and doctor**
- » **Prohibited behaviors, and grounds for tapering or discontinuation**
- » **Limitations on prescriptions**
- » **Emergency issues**
- » **Refill and dose-adjustment procedures**
- » **Exit strategy**

Sample agreement available in the Opioid Analgesic Tool Kit.

*Patient Agreement*

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The “opioid therapy patient agreement” has been developed to help address some of these issues and concerns. Opioid agreements are intended to improve adherence to therapy and to enhance therapeutic relationships by initiating an alliance between the patient and the physician.

Opioid agreements may vary distinctly in tone and demeanor. The language in which some agreements are couched is designed to invoke a sense of cooperation and equality. These agreements often devote considerable space to explanations of their utility and value. They stress the rights and responsibilities of both the healthcare provider and the patient. They offer broad, generalized, and nonconfrontational guidelines and avoid proscriptions or commandments. Other agreements are more dogmatic in tone. Their language is more authoritative, more concerned with the presentation of detailed rules and procedures. These agreements tend to outline specific consequences for breaking the agreement, and usually contain less in the way of educational information.

Each type of agreements offers advantages and each may entail certain disadvantages. The more equitable, less confrontational agreements enable patients to feel they are taking a more active role in their therapy—the sort of perception that may serve to improve compliance. On the other hand, the broader, less explicit language featured in these agreements might decrease compliance—because the patient has not been given strict, unambiguous rules to follow.

The more dogmatic, rule-giving agreements may have the advantage of laying down very clear guidelines, but they may make the patient feel he or she is not trusted, or is not being treated as a rational, decision-making adult. Such agreements may also unwittingly stigmatize opioids by fostering the impression that opioid use is bad or dangerous.

Fishman SM, Bandman BA, Edwards A, Borsook D. The opioid contract. *J Pain Symptom Manage*. 1999;18:27-37

The screenshot shows a software application window titled "NIPC". At the top, there is a horizontal menu bar with six items: "Patient Selection", "Patient Selection Vignettes", "Trial of Opioids", "Trial of Opioids Vignettes", "Patient Reassessment", and "Reassessment Vignettes". Below the menu bar, the main content area has a title "Initiating Opioid Therapy". A large text box contains the following message: "You've made the decision to prescribe opioid analgesics for your patient. Now you must:" followed by a bulleted list of three items. At the bottom of the window, there is a toolbar with several buttons: "70", "SUMMARY", "COOL IT", "PRINT", and "HOME MENU".

**You've made the decision to prescribe opioid analgesics for your patient. Now you must:**

- » Consider cost, tolerability, ease of administration, compliance
- » Decide whether to start a short-acting opioid analgesic or a low dose of a long-acting opioid analgesic, with or without short-acting "rescue" doses if breakthrough pain occurs
- » Develop and document an Exit Strategy

For moderate to severe pain unresponsive to nonopioid analgesia, the WHO ladder recommends “weak” opioids such as codeine or meperidine. Meperidine, however, is more likely to be restricted to breakthrough pain; although it is fast-acting, chronic use is contraindicated because of its conversion to the toxic metabolite normeperidine, which may cause seizures.

For refractory severe pain, the WHO ladder recommends “strong” opioids such as morphine, oxycodone, hydromorphone, or methadone.

Dalton JA, Youngblood R. Clinical application of the World Health Organization Analgesic Ladder. *J Intraven Nur.* 2000;23:118-124.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NPC**

## Opioids in Chronic Pain: Review of Randomized, Controlled Clinical Trials

Efficacy of opioids in chronic non-cancer pain has been established in a number of randomized, controlled trials, including placebo-controlled trials, of:

- » Codeine
- » Fentanyl
- » Levorphanol
- » Methadone
- » Morphine
- » Oxycodone
- » Oxymorphone
- » Tramadol

7.1

SUMMARY

CONTINUE

HOME

SEARCH

The efficacy of opioids in chronic pain has been established in a number of randomized, controlled trials, including placebo-controlled trials of controlled-release oral codeine,<sup>1,2</sup> and tramadol,<sup>3</sup> immediate- and sustained-release oxycodone,<sup>4-6</sup> intravenous and sustained-release oral morphine,<sup>7-11</sup> fentanyl,<sup>12</sup> and levorphanol.<sup>13</sup>

In a comparison of transdermal vs oral delivery, transdermal fentanyl and sustained-release oral morphine were compared in a crossover trial. In this study, a significantly greater number of patients (35% vs 23%;  $P=.002$ ) considered pain control better with transdermal fentanyl than with morphine.<sup>8</sup>

1. Peloso PM, Bellamy N, Bensen W. Double blind randomized placebo controlled trial of controlled release codeine in the treatment of osteoarthritis of the hip and knee. *J Rheumatol.* 2000;27:764-771.
2. Arkinstall W, Sandler A, Goughnour B, Babul N, Harsany Z, Darke A. Efficacy of controlled-release codeine in chronic non-malignant pain. *Pain.* 1995;62:169-178.
3. Harati Y, Gooch C, Swenson M, et al. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. *J Diabetes Complications.* 2000;14:65-70.
4. Roth SH, Fleishman RM, Burch FX, et al. Around-the-clock controlled release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med.* 2000;160:853-860.
5. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol.* 1999;26:862-869.
6. Watson CPN, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology.* 1998;50:1837-1841.
7. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol.* 1999;26:862-869.
8. Allan L, Hays H, Jensen N-H, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *Br Med J.* 2001;322:1-7.
9. Jamison RN, Raymond SA, Slawsky EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer backpain. A randomized prospective study. *Spine.* 1998;23:2591-2600.
10. Moulin DE, Iezzi A, Amireh R, et al. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147.
11. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology.* 1991;41:1024-1028.
12. Dellemijn PL, Vanneste JA. Randomized double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. *Lancet.* 1997;349:753-758.
13. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med.* 2003;348:1223-1232.

Additional References

- Gabrail NY, Dvergsten C, Ma T, Frailey A, Ahdieh H. Oxymorphone extended release (ER) provides safe and effective and rapid analgesia during opioid rotation: Results of a randomized, double-blind, crossover, comparative study with oxycodone controlled-release (CR). Proceedings ASCO 22:2003;737 [abstract 2962].
- Hale M, Dvergsten C, Kurkimilis E, Ahdieh H. Oxymorphone extended release (ER) provides equianalgesia at half the dose compared with oxycodone controlled release (CR) in chronic low back pain: results of a randomized double-blind, placebo-controlled study. 22nd Annual Meeting of the American Pain Society, Chicago, IL, March 2003 [abstract 828]. *J Pain.* 2003;4(suppl 1):58.
- McIlwain H, Burch F, Frailey A, Ma T, Ahdieh H. Oxymorphone extended-release offers long-term safety, effectiveness, and dose stabilization in osteoarthritis pain: results of a one-year interim report. 22nd Annual Meeting of the American Pain Society, Chicago IL, March 2003 [Abstract 908]. *J Pain.* 2003;4(suppl 1):78.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NIPC**

## Short-acting Opioids

- » **Codeine\***
- » **Fentanyl (oral transmucosal fentanyl citrate) (Actiq, Fentora)**
- » **Hydrocodone (eg, Zydome, Vicodin, Lortab, Loracet, Norco, Vicoprofen and others)\***
- » **Hydromorphone (Dilaudid)**
- » **Morphine sulfate (eg, Roxanol, MSIR)**
- » **Oxycodone (eg, Roxicodone, Oxy IR, Percocet, Tylox, Percodan)\***
- » **Oxymorphone (Numorphan, Opana)**
- » **Tramadol (Ultram, Ultracet)\***

\*May contain additional active ingredient.  
See Tool Kit for a comprehensive table of Opioid Analgesics.  
*Opioid Analgesics Table*

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Short-acting opioids are appropriate for treatment of acute pain or breakthrough/incident pain, whereas long-acting formulations are used for patients with continuous chronic pain. Short-acting agents provide effective analgesia for acute pain but should be avoided as primary analgesics for chronic pain management, eg, the short-acting opioid meperidine is inappropriate for chronic pain analgesia because of its conversion to the toxic metabolite normeperidine, which can cause seizures. Short-acting opioids may be used during the initial dose titration period of long-acting formulations and as rescue medication for episodes of breakthrough/incidence pain.<sup>1,2</sup>

Some short- and long-acting opioids may also contain other analgesics (eg, oxycodone/acetaminophen, hydrocodone/ibuprofen), and the recommended maximal limits of such agents should be considered.

1. American Geriatric Society. Clinical Practice Guidelines. The management of chronic pain in older persons. *J Am Geriatr Soc.* 1998;46:635-651.

2. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001;8:181-186.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NIPC**

## Long-acting Opioids

- » Levorphanol (Levo-Dromoran)
- » Methadone (Dolophine, Methadose)
- » Oxymorphone extended release (Opana ER)
- » Sustained-release morphine (eg, MS Contin, Avinza; Kadian, Oramorph SR, Morphine ER)
- » Sustained-release oxycodone (Oxycontin)
- » Tramadol extended release (Ultram ER)
- » Transdermal fentanyl (Duragesic)

See Tool Kit for a comprehensive table of Opioid Analgesics.  
[Opioid Analgesics Table](#)

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Long-acting opioids have greater utility than short-acting opioids in treating chronic pain in patients with consistent pain levels. Long-acting, controlled-release, oral formulations of opioids (eg, morphine, oxycodone), which have a predictable duration of action lasting from 8 to 12 hours, make around-the-clock therapy possible, offering dosing convenience, flexibility, and relatively steady opioid concentrations in the blood.<sup>1,2</sup>

Opioid treatment should be initiated using a short-acting formulation. In general, short-acting formulations allow for more immediate pain relief and assist in establishing the effective dose range of the agent. For patients with chronic pain, once the minimal effective analgesic daily dose is achieved, the treatment plan should include switching to a long-acting opioid.<sup>2</sup>

1. American Geriatric Society. Clinical Practice Guidelines. The management of chronic pain in older persons. *J Am Geriatr Soc.* 1998;46:635-651.

2. McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001;8:181-186.



**Longer Acting Opioid Dosage Forms**

Pharmacologically Long Acting	Pharmaceutically Long Acting
<ul style="list-style-type: none"><li>◦ <b>Levorphanol</b><ul style="list-style-type: none"><li>– Levo-Dromoran</li></ul></li><li>◦ <b>Methadone</b><ul style="list-style-type: none"><li>– Dolophine</li><li>– Methadose</li></ul></li></ul>	<ul style="list-style-type: none"><li>◦ <b>Extended-release oxymorphone</b><ul style="list-style-type: none"><li>– Opana ER</li></ul></li><li>◦ <b>Sustained-release morphine</b><ul style="list-style-type: none"><li>– Oramorph SR, MS Contin, Kadian, Avinza, Morphine ER</li></ul></li><li>◦ <b>Sustained-release oxycodone</b><ul style="list-style-type: none"><li>– OxyContin</li></ul></li><li>◦ <b>Transdermal Fentanyl</b><ul style="list-style-type: none"><li>– Duragesic</li></ul></li></ul>

74      **SUMMARY**      EXIT      HELP      HOME MENU

This is a different approach to the previous slide in that it distinguishes between drugs with a long half-life versus those formulated for sustained action.

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NIPC**

## Newly Approved Opioids

Generic Name	Brand Name	Available Doses	Indication	Contraindications	Additional Information
Fentanyl Buccal Tablet (Approved 9/25/05)	Fentora	100, 200, 400, 600, 800 mcg	Breakthrough pain in opioid-tolerant cancer patients	Management of acute or postoperative pain and in opioid non-tolerant patients	Titrate with caution in elderly and patients with COPD and bradycardias
Oxymorphone Hydrochloride Tablet (Approved 6/22/05)	Opana (immediate-release formulation)	5, 10 mg	Moderate to severe acute pain	Patients with moderate to severe hepatic impairment	Use with caution in elderly and patients with renal impairment
Oxymorphone Hydrochloride Extended-release Tablet (Approved 6/22/05)	Opana ER (extended-release formulation)	5, 10, 20, 40 mg	Moderate to severe pain in patients requiring continuous opioid analgesia	Patients with moderate to severe hepatic impairment. Also contraindicated for immediate post-op period and mild pain	Use with caution in elderly and patients with renal impairment

Fentora [package insert]; Opana [package insert]; Opana ER [package insert]

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- Cephalon Receives FDA Approval of FENTORA(TM) (fentanyl buccal tablet) for the Management of Breakthrough Pain in Patients with Cancer. Available at: [. Accessed October 16, 2006.](http://phx.corporate-ir.net/phoenix.zhtml?c=81709&p=irol-newsArticle&ID=908959&highlight=)

- Endo Announces Commercial Availability of Opana(R) ER (oxymorphone HCl) Extended-Release and Opana(R) (oxymorphone HCl) Immediate-Release Tablets CII. [. Accessed October 16, 2006.](http://phx.corporate-ir.net/phoenix.zhtml?c=123046&p=irol-newsArticle&ID=885302&highlight=)

The screenshot shows a web-based educational module. At the top, there is a horizontal navigation bar with six tabs: "Patient Selection", "Patient Selection Vignettes", "Trial of Opioids", "Trial of Opioids Vignettes", "Patient Reassessment", and "Reassessment Vignettes". Below this is a vertical sidebar on the left labeled "NIPC" with a small logo. The main content area has a title "Methadone Considerations\*" in bold. Underneath the title is a bulleted list of 12 points describing methadone's properties and potential risks. At the bottom of the main content area, there is a note: "\*Consultation with specialist strongly recommended." Below the main content area is a footer bar with icons for "SEARCH", "HOME", "HELP", "LOGOUT", and "PRINT MENU".

- » **Possible dual mechanism of action**
  - opioid and non-opioid effects
- » **Relatively inexpensive**
- » **Available as a liquid**
- » **Long half-life**
  - accumulates with repeat doses with limited analgesic effect
- » **Complex pharmacokinetics**
- » **No known active metabolites**
- » **Conversion tables underestimate potency**
- » **Cardiac toxicity with high doses or with CYP3A4 inhibitors**
- » **Adverse interaction with TCAs**

\*Consultation with specialist strongly recommended.

**Because of methadone's long half life (15-30 hours), with drug accumulation over several days, methadone needs to be administered with caution with long intervals between dose adjustments (5-7 days).** There have been deaths reported with the use of methadone for chronic pain. Although details are often unclear, many of these deaths may be due to conversion of patients from other opioids to methadone. Methadone has been associated with QRS prolongation, which can lead to sudden cardiac death. If unfamiliar with the use of methadone, it is advisable to seek consultation with a pain specialist, especially when considering prescribing more than low-dose methadone (20-30 mg/day).

The l-isomer of methadone possesses opioid activity, whereas the d-isomer is weak or inactive as an opioid. Both d- and l-methadone have been shown to bind to the N-methyl-D-aspartate (NMDA) receptor. There is some evidence that d-methadone is antinociceptive as a result of its NMDA receptor antagonist activity.

Drug Facts and Comparisons. Ed 58. Narcotic Agonist Analgesics. Wolters Kluwer Health, St Louis, 2004, 902, 914.

Hall W, Lynskey M, Degenhardt L. Trends in opiate-related deaths in the United Kingdom and Australia, 1985-1995. *Drug Alcohol Depend*. 2000;57:247-254.

Milroy CM, Forrest AR. Methadone deaths: a toxicological analysis. *J Clin Pathol*. 2000;53:277-281.

Shimoyama N, Shimoyama M, Elliott KJ, Inturrisi CE. d-Methadone is antinociceptive in the rat formalin test. *J Pharmacol Exp Ther*. 1997;283:648-652.

Email communications from Lori Reisner, October 6, 2003, January 30, 2004, and February 4, 2004.

Email communications from Charles Argoff, February 3, 2004.

Email communications from Richard Payne, February 4, 2004.

The screenshot shows a slide from the NIMH Opioid Research Toolkit. The top navigation bar includes tabs for Patient Selection, Patient Selection Vignettes, Trial of Opioids, Trial of Opioids Vignettes, Patient Reassessment, and Reassessment Vignettes. The slide title is "Methadone Drug Interactions". The main content lists interactions with CYP enzymes and enzyme inducers:

- « Major substrate of hepatic cytochrome P450 (CYP) 3A4
  - also weak inhibitor
- « Minor/weak substrate of CYP2C8/9, CYP2C19, CYP2D6
  - moderately inhibits CYP2D6
- « Enzyme inducers: barbiturates, carbamazepine, phenytoin, primidone, and rifampin
  - may decrease serum methadone concentrations via enhanced hepatic metabolism
  - monitor for methadone withdrawal; larger doses of methadone may be required

At the bottom of the slide, there are links for Summary, Cite, Print, and Email.

Methadone is metabolized primarily by CYP3A4, secondarily by CYP2D6, and to a smaller extent by CYP1A2 and additional enzymes that are under study

CYP3A4, the most abundant metabolic enzyme in the body, can vary 30-fold between individuals in terms of its presence and activity in the liver.<sup>1</sup> This enzyme also is found in the gastrointestinal tract, so methadone metabolism actually starts before the drug enters the circulatory system.<sup>2</sup>

The amount of this enzyme in the intestine can vary up to 11-fold, partially accounting for variable breakdown of methadone.<sup>3</sup>

1. Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P. When 'enough' is not enough: new perspectives on optimal methadone maintenance dose. *Mt Sinai J Med.* 2000;67(5-6):404-411.
2. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill; 1996:3-63.
3. Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds). *Metabolic Drug Interactions*. Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

The screenshot shows a section titled "Methadone Drug Interactions (cont'd)". A bulleted list details various drug interactions:

- « **Cytochrome (CYP) 3A4 inhibitors: serum level and/or toxicity of methadone may be increased**
  - cardiovascular: amiodarone, diltiazem, verapamil
  - anti-infective: clarithromycin, erythromycin, dirithromycin, itraconazole, ketoconazole, metronidazole, quinupristin-dalfopristin
  - anti-viral: delavirdine, indinavir, nevirapine, ritonavir, saquinavir
  - CNS: fluoxetine, fluvoxamine, nefazodone, propoxyphene
  - miscellaneous: cimetidine, disulfiram, zafirlukast, zileuton

At the bottom of the page, there are navigation links: "78", "SUMMARY", "CONTINUE", "PREVIOUS", and "HOME MENU".

When co-prescribing medications with methadone, either enzyme induction or inhibition is involved.

CYP-enzyme **inhibitors** may slow methadone metabolism, raise the serum methadone level, extend the duration of its effects, and possibly cause methadone-related toxicity.

Zidovudine (AZT) AZT concentration increases 40% with methadone; more frequent AZT side effects are possible.<sup>1</sup>

1. McCance-Katz EF, Jatlow P, Rainey P, Friedland G. Methadone effects on zidovudine (AZT) disposition (ACTG 262). *J Acquir Immune Defic Syn Hum Retrovirol*. 1998;18:435-443.

The screenshot shows a section of the NIMC website titled "Methadone Drug Interactions (cont'd)". The page has a header with tabs: Patient Selection, Patient Selection Vignettes, Trial of Opioids, Trial of Opioids Vignettes, Patient Reassessment, and Reassessment Vignettes. A logo for NIMC is in the top left. Below the title is a bulleted list of drug interactions:

- » Somatostatin: methadone efficacy may be decreased; limited documentation
- » Zidovudine: serum concentrations may be increased by methadone
- » May compound QTc prolongation with other drugs that affect ventricular rate

At the bottom of the page are navigation links: 79, SUMMARY, COOL SITE, PREVIOUS, and HOME PAGE.

When co-prescribing medications with methadone, either enzyme induction or inhibition is involved.

CYP-enzyme **inhibitors** may slow methadone metabolism, raise the serum methadone level, extend the duration of its effects, and possibly cause methadone-related toxicity.

Zidovudine (AZT) AZT concentration increases 40% with methadone; more frequent AZT side effects are possible.<sup>1</sup>

1. McCance-Katz EF, Jatlow P, Rainey P, Friedland G. Methadone effects on zidovudine (AZT) disposition (ACTG 262). *J Acquir Immune Defic Syn Hum Retrovirol*. 1998;18:435-443.

**Methadone Food/Herbal Interactions**

- » **Ethanol**
  - avoid ethanol: may increase CNS effects; watch for sedation
- » **Herbal/Nutraceutical: avoid concurrent**
  - St John's wort: may decrease methadone levels; may increase CNS depression
  - valerian, kava kava, gotu kola: may increase CNS depression
  - grapefruit Juice: may increase methadone levels and CNS depression via CYP3A4 in the intestines

Ethanol (*chronic use*)

wine, beer, whiskey, etc  
euphoric, sedative  
induces P450 enzyme<sup>1</sup>

St. John's wort (*Hypericum perforatum*)

ingredient in various OTC products  
herb used as antidepressant  
induces CYP 3A4; 47% decrease in methadone <sup>2-3</sup>

Grapefruit juice

inhibits intestinal CYP3A4<sup>4</sup> (Hall et al. 1999) and PgP<sup>5</sup>  
this effect is not expected with other fruits/juices<sup>6</sup>

1. Quinn DI, Wodak A, Day RO. Pharmacokinetic and pharmacodynamic principles of illicit drug use and treatment of illicit drug users. *Clin Pharmacokinet.* 1997;33(5):344-400.

2. Eich-Höchli D, Oppiger R, Golay KP, Baumann P, Eap CB. Methadone maintenance treatment and St. John's wort. *Pharmacopsychiatry.* 2003;36:35-37.

3. Scott GN, Elmer GW. Update on natural product-drug interactions. *Am J Health Syst Pharm.* 2002;59(4):339-347.

4. Hall SD, Thummel KE, Watkins PB. Molecular and physical mechanisms of first pass extraction. *Drug Metab Disp.* 1999;27:161-166.

5. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet.* 2002;41:1153-1193.

6. Karlix J. Pharmacists Corner [untitled discussion on fruit juice and medication levels in blood serum]. Prescription Plus. Ronkonkoma, NY: Lifecare Pharmaceuticals Services; 1990:15.

The screenshot shows a software application window titled "NIPC Opioid Analgesics Toolkit". At the top, there is a horizontal menu bar with six items: "Patient Selection", "Patient Selection Vignettes", "Trial of Opioids", "Trial of Opioids Vignettes", "Patient Reassessment", and "Reassessment Vignettes". Below the menu, the main content area has a title "Create an Exit Strategy". The content is organized into bullet points:

- » Upon initiating opioid therapy, agree with patient on criteria for failure of the trial
- » Common failure criteria include:
  - lack of significant pain reduction
  - lack of improvement in function
  - persistent side effects
  - persistent noncompliance
- » Document method for tapering off opioids if trial is not successful

In the center of the page, there is a note: "A comprehensive Exit Strategy Guide is available in the Opioid Analgesics Tool Kit." Below this note, there is a link labeled "Exit Strategy Guide". In the bottom right corner of the main content area, there is a small rectangular box containing the text "END OF PAGE".

At the very bottom of the window, there is a navigation bar with several buttons: "HOME", "CONTINUE", "PREVIOUS", "NEXT", and "MAIN MENU".

One of the most difficult aspects of long-term opioid therapy is recognizing which patient has not responded well to opioids, and deciding how to take that patient off opioid therapy. It is essential that an exit strategy be discussed with the patient when initiating a trial of opioid therapy and that there is agreement on all criteria that will be considered. Most important of these are insufficient pain reduction, failure of the patient on the trial to improve functionality and performance of essential activities of daily living, the persistence or increase of side effects, and the noncompliance of the patient to adhere to the opioid trial regimen.

It is also important for the physician to document the method followed in tapering off the opioid analgesics if the trial is not successful. In order to facilitate this process, a simple **exit strategy algorithm** has been developed and is available for downloading from the Opioid Analgesia CD-ROM. The algorithm will guide you in identifying the opioid non-responder, and in broad terms, what your options are for tapering the patient off opioid therapy.

Patient Selection   Patient Selection Vignettes   Trial of Opioids   Trial of Opioids Vignettes   Patient Reassessment   Reassessment Vignettes

**Drug Safety: 78-yr-old Woman With Osteoarthritis**

NPC

- » 78-yr-old woman with osteoarthritis of the knees and hips
- » You are trying to choose the best analgesic for her



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Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

**What Form of Drug Therapy Would You Recommend?**

1. Nonselective NSAID  
2. Cox-2 selective NSAID  
3. Immediate-release opioid analgesic  
4. Extended-release opioid analgesic  
5. Topical analgesic



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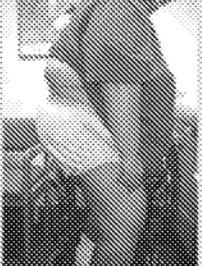
MAIN MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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NIPC

## Case Presentation: Meet Roberta K

- » **59-yr-old woman with disabling chronic low back pain**
- » **Diabetes, obesity, hypertension, mild renal insufficiency, peripheral neuropathic pain in feet**
- » **Depends on wheelchair**
  - does not ambulate
- » **Satisfactory control of feet pain with gabapentin 800 mg bid**
- » **No history of drug abuse**



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SEARCH

REFRESH

HOME MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

**NIPC**

Considering the Risks/Benefits Associated With the Following Classes of Drugs, Which Would You Recommend for Roberta K?

1. NSAIDs  
2. Opioids  
3. Antidepressants  
4. Anticonvulsants  
5. Topical agents

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PREVIOUS

NEXT

HOME MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

**NIPC**

## Questions to Consider Before Initiating a Trial of Opioid Therapy for Roberta K

- » Are opioids effective in chronic non-cancer pain?
- » Do comorbidities influence choice of analgesic class?
- » Does life expectancy of patient influence choice of analgesic class?
- » Does patient's inability to ambulate influence the prescribing of opioids?

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SEARCH

HOME

ABOUT

CONTACT

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

NIPC

## Modifying Therapy: Roberta K

- » Roberta reports almost no pain improvement on morphine SR 30 mg bid
- » Complains of constipation
- » Still using wheelchair rather than walking
- » What do you do now?

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PREVIOUS PAGE

NEXT PAGE

HOME MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

**NIPC**

## Modifying Therapy: What Do You Do Now?

- 1. Raise dose of opioid
- 2. Change opioid
- 3. Use adjuvant
- 4. Do urine screen
- 5. Add laxative

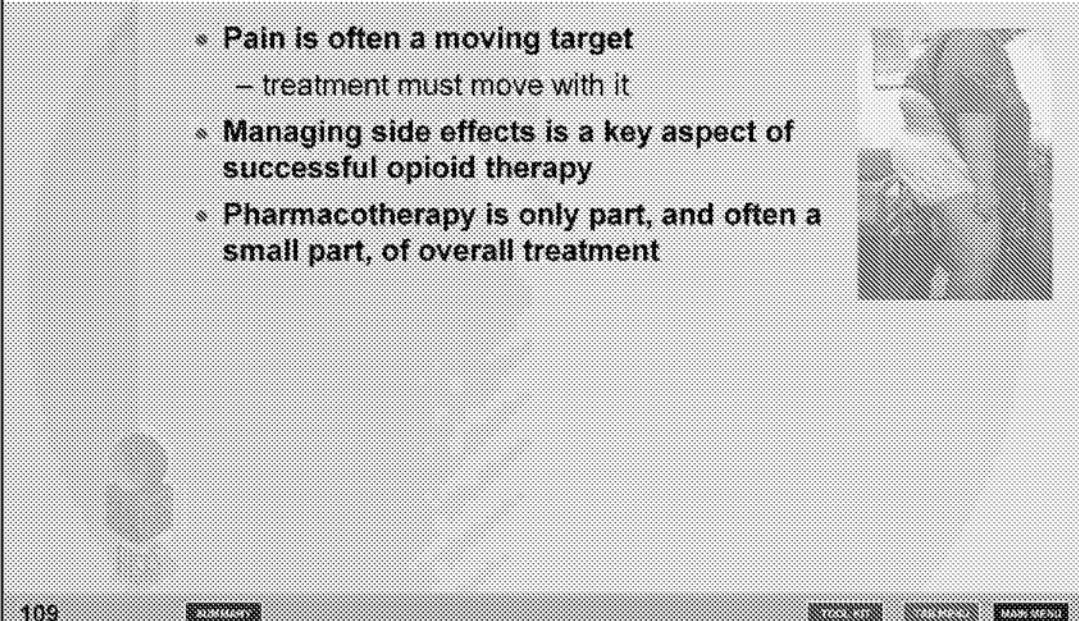
108

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

NIPC

## Modifying Therapy: Considerations

- « Pain is often a moving target
  - treatment must move with it
- « Managing side effects is a key aspect of successful opioid therapy
- « Pharmacotherapy is only part, and often a small part, of overall treatment



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SEARCH

REVIEW

MAPS

HOME MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

NIPC

## Opioid Therapy Modification: Roberta K

- » On oxycodone CR 20 mg bid, Roberta is out of wheelchair 50% of time
- » Constipation remains a problem despite senna tablets bid
- » She has not complied with recommendation for physical therapy
- » Urine screen shows no opioid

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SEARCH

PRINT

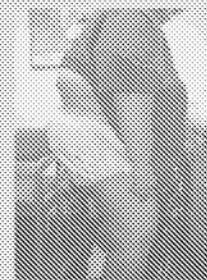
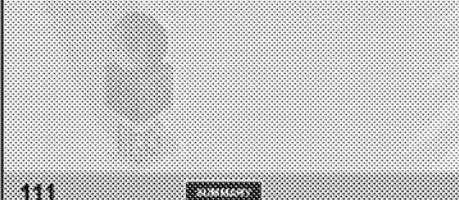
HOME MENU

Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
-------------------	-----------------------------	------------------	----------------------------	----------------------	------------------------

**NIPC**

## Questions to Consider in Modifying a Trial of Opioid Therapy for Roberta K

- » When should opioid dose be raised?
- » When should a different opioid be tried?
- » What factors guide the choice of a second opioid?
- » How reliable are urine screenings?



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QUESTION

ANSWER

ANSWER

ANSWER

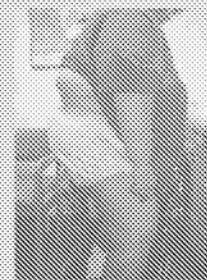
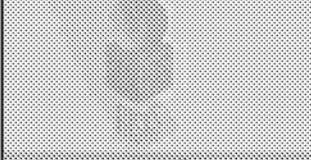
Patient Selection	Patient Selection Vignettes	Trial of Opioids	Trial of Opioids Vignettes	Patient Reassessment	Reassessment Vignettes
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**NIPC**

## What Is Success?

### Case Study: Roberta K

- » Doses of oxycodone higher than 20 mg bid make her feel sleepy
- » Increasing dose of senna to 2 tablets bid relieves constipation
- » She is still out of wheelchair 50% of time
- » She says you're the best doctor she's ever had
- » What do you do now?



END OF CASE

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SEARCH

RECALL

MAPS MENU

The screenshot shows a presentation slide titled "Initiating a Trial of Opioid Therapy Key Points". The slide has a black header bar with tabs: "Patient Selection", "Patient Selection Vignettes", "Trial of Opioids", "Trial of Opioids Vignettes", "Patient Reassessment", and "Reassessment Vignettes". Below the header is a logo for "NIPPC" with a stylized "P" icon. The main content area contains a bulleted list of key points:

- » *Determine Treatment Goals*
- » *Select Most Appropriate Opioid Therapy*
  - *Short- vs Long-acting Opioids*
  - *Methadone Considerations*
- » *Prepare an Exit Strategy*

At the bottom of the slide are three small buttons labeled "PREVIOUS", "NEXT", and "HOME PAGE".

Nociceptive, inflammatory, and neuropathic pain may result from diverse mechanisms. Some of these mechanisms are unique to one painful condition; others are present in multiple clinical syndromes, or may be expressed at different times during the natural history of a syndrome. The same symptom (eg, pain in response to light touching of the skin) may be generated by a number of mechanisms; or a single mechanism (eg, upregulation of a voltage-gated sodium channel) may potentially produce different symptoms—such as spontaneous burning pain, shock-like pain, or paresthesias.

Structural alterations in the synaptic contacts of low-threshold afferents with pain transmission neurons, or a reduction of inhibitory mechanisms due to a loss of interneurons, may represent persistent changes in the central nervous system that eventually result in a fixed state of sensitization.

Back pain is ubiquitous and probably plagues almost everyone in all cultures and ethnic groups at some time. While it may be that precise estimates of the prevalence of neuropathic pain are not readily available, chronic neuropathic pain may be much more common than has been generally appreciated and can be expected to increase in the future. Moreover, neuropathic pain is highly prevalent in patients with cancer. Chronic widespread pain, the cardinal symptom of fibromyalgia, is common in the general population, with comparable prevalence rates of 7.3% to 12.9% across different countries.

Effective management of chronic pain has become an increasingly critical issue in health care. Studies have shown that chronic pain is a common, persistent problem in the community, with relatively high incidence and low recovery rates.

Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain*. 2002;18:343-349.

Ehrlich GE. Back pain. *J Rheumatol Suppl*. 2003;67:26-31.

Elliott AM, Smith BH, Hannaford PC, Smith WC, Chambers WA. The course of chronic pain in the community: results of a

4-year follow-up study. *Pain*. 2002;99:299-307.

Katz N. Neuropathic pain in cancer and AIDS. *Clin J Pain*. 2000;16(suppl 2):S41-S48.

Neumann L, Buskila D. Epidemiology of fibromyalgia. *Curr Pain Headache Rep*. 2003;7:362-368.

Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5(suppl):S1062-S1067.

